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Synthesis and Insecticidal Activity of Novel Pyrazole Methanesulfonates*

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Abstract: A model has been used to design novel pyrazole methanesulfonates. The pyrazole carboxamide methanesulfonates demonstrated insecticidal activity with low levels of acute mammalian toxicity. The amides formed from amines with α-branching (e.g. isopropyl and *sec*-butyl) demonstrated the highest level of activity. The model has also been used to design novel pyrazole sulfonamide methanesulfonates with very high levels of insecticidal activity. Most of the sulfonamides also possessed significant acute mammalian toxicity. Rice paddy field testing of the carboxamides on field population hoppers gave poor results.

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Key words: insecticide, acetylcholinesterase, methanesulfonate, pyrazole, synthesis

1 INTRODUCTION

In our previous work[1] we developed a model (Fig. 1, **I**) which helped us design and synthesize 6-methanesulfonyloxypyridine-2-carboxamides with insecticidal activity and low mammalian toxicity. This model also predicted high levels of insecticidal activity for heterocycles other than pyridines. In this paper we discuss the design and synthesis of highly insecticidal pyrazole methanesulfonates.

The biological aim of our previous work was the discovery of a rice insecticide. In the present effort we still maintained that goal, but we were also looking for a soil insecticide. Soil insecticides are generally incorporated in the soil with the planting of the crop, so to be useful, a compound must provide season-long root protection with a single application. In that regard we were encouraged by the report of Kato *et al.*[2] of compound **II**. In our greenhouse tests compound **II** demonstrated high levels of root protection in soil.

Our model requires a nitrogen heterocycle with a methanesulfonate group on one side of the nitrogen atom and on the other side a branched lipophilic sidechain containing an oxo-substitution. It can be seen that 1,3-substituted pyrazoles of formula **III** fit our model and are thus predicted to be highly insecticidal. These compounds became our primary targets, but for ease of synthesis we chose to synthesize 1,5-substituted pyrazoles (**IV**) first.

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2 MATERIALS AND METHODS

2.1 Synthesis of compounds

The synthesis scheme used to prepare 1,5-substituted pyrazoles is shown in Fig. 2. The appropriate semicarbazide or sulfonylhydrazide was condensed with a β-ketoester in the presence of an equivalent of sodium ethoxide. The methanesulfonates were prepared by reaction of the resulting pyrazolone with methanesulfonyl chloride in the presence of triethylamine in dichloromethane.

The synthesis schemes used to prepare 1,3-substituted pyrazoles are shown in Fig. 3. Initially we employed the method of Drummond and Johnson[3] to prepare 5-amino-3-hydroxypyrazoles and removed the amino group by diazotization. Later, after discovering the hydrolytic instability of the 1,5-substituted pyrazoles (see below) we discovered that pyrazole methanesulfonate esters lacking a substituent on nitrogen

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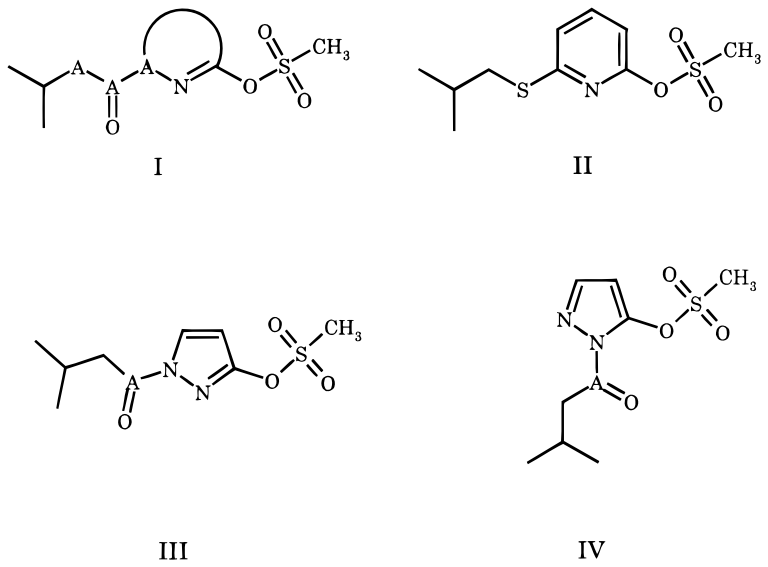
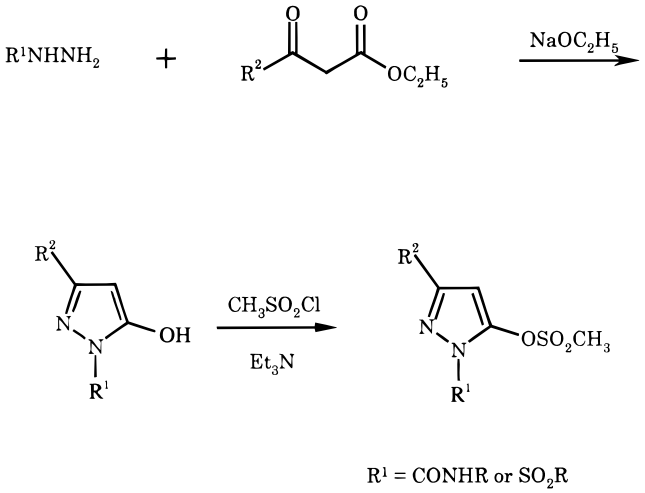


I II III IV

Fig. 1. Structures of compounds discussed.

reacted selectively to give the 1,3-isomers. The unsubstituted compounds were prepared by reaction of the appropriate pyrazolone with methanesulfonyl chloride in the presence of triethylamine in dichloromethane. (A small amount of the pyrazolone reacted with two equivalents of methanesulfonyl chloride. This by-product could be removed by column chromatography.) Representative procedures are given below.



$R^1 = CONHR$ or SO_2R

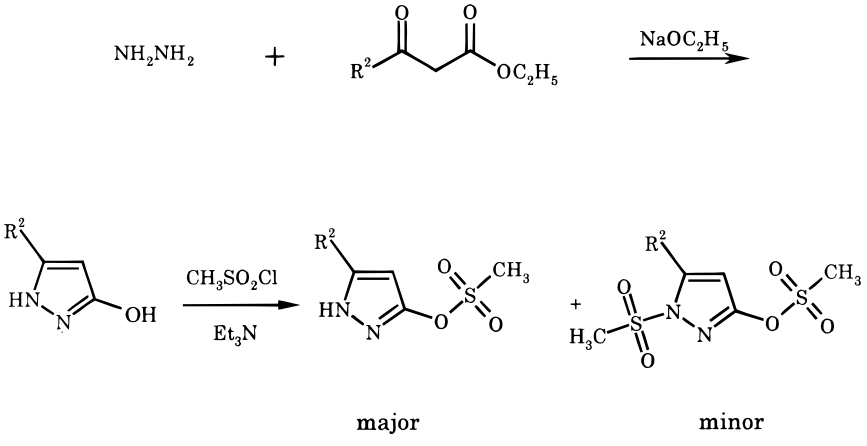
Fig. 2. Synthesis of 1,5-substituted pyrazoles.

2.1.1 1,5-Substituted pyrazoles

2.1.1.1 N-*Isopropyl-5-hydroxy-3-methyl-1*H-*pyrazole-1-carboxamide.* To a solution of 4-isopropylsemicarbazide (4·0 g, 34 mmol) in ethanol (75 ml) was added ethyl acetoacetate (4·3 ml, 34 mmol) and a solution of sodium ethoxide in ethanol (2·68 M; 12·7 ml ≡ 34 mmol). The reaction mixture was heated to reflux overnight. The solvent was then removed with a rotary evaporator, the residue taken up in a minimum of water and acidified with concentrated hydrochloric acid. The resulting solid was filtered off and washed with a small amount of ethyl acetate to give 4·73 g of the title compound as a tan solid after drying in a vacuum oven; m.p. 163–4°C.

[^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 1·17 (d, 6), 2·12 (s, 3), 3·90 (m, 1), 5·07 (br, 1), 8·82 (brd, 1), 12·3 (br, 1).

2.1.1.2 N-*Isopropyl-3-methyl-5-methanesulfonyloxy-1*H-*pyrazole-1-carboxamide* (*2*). To a solution of *N*-isopropyl - 5 - hydroxy - 3 - methyl - 1*H* - pyrazole - 1 - carbox -



major minor

Fig. 3. Synthesis of 1,3-substituted pyrazoles.

amide (1·0 g, 5·5 mmol) in dichloromethane (35 ml) at 0°C was added triethylamine (1·1 ml, 7·7 mmol) followed by methanesulfonyl chloride (0·60 ml, 7·7 mmol). The reaction mixture was stirred at room temperature overnight, then washed with water, dried (sodium sulfate), filtered and the solvent removed with a rotary evaporator. The residue was purified by flash chromatography on silica gel (ethyl acetate + hexane, (25 + 75 by volume) as eluant) to afford 0·77 g of **2** as a colorless oil.

[^{1}H]NMR (deuterochloroform): δ 1·27, (d, 6), 2·24 (s, 3), 3·90 (s, 3), 4·05 (m, 1), 6·07 (s, 1), 6·93 (br, 1).

2.1.2 1,3-Substituted pyrazoles

*2.1.2.1 1*H-*Pyrazol-3-yl methanesulfonate.* To a solution of 1*H*-pyrazol-3-ol (16·58 g, 0·197 mol) in THF (500 ml) at 0°C was added triethylamine (30·3 ml, 0·217 mol) followed by dropwise addition of methanesulfonyl chloride (16·8 ml, 0·217 mol). The reaction mixture was stirred at room temperature overnight. After filtration the solvent was removed with a rotary evaporator. The residue was dissolved in dichloromethane, washed with water, dried (sodium sulfate), filtered and the solvent removed with a rotary evaporator. The residue was purified by flash chromatography on silica gel (THF + dichloromethane (5 + 95 by volume) as eluant) to afford 17·77 g of the title compound as a white solid; m.p. 63–65°C.

[^{1}H]NMR (deuterochloroform): δ 3·30 (s, 3), 6·21 (s, 1), 7·53 (s, 1), 10·05 (br, 1).

2.1.2.2 N-*Isopropyl-3-methanesulfonyloxy-1*H-*pyrazole-1-carboxamide* (***11***). To a solution of 1*H*-pyrazol-3-yl methanesulfonate (5·0 g, 31 mmol) in THF (150 ml) was added isopropylisocyanate (6·1 ml, 62 mmol). The reaction mixture was heated to reflux for three days with further isopropylisocyanate (3 ml, 30 mmol) being added each day. At the end of the reaction the solvent was removed with a rotary evaporator. The residue was purified by flash chromatography (ethyl acetate + hexane (25 + 75 by volume) as eluant) to afford 7·17 g of **11** as a white solid; m.p. 93–94°C.

[^{1}H]NMR (deuterochloroform): δ 1·29 (d, 6), 3·31 (s, 3), 4·12 (m, 1), 6·31 (s, 1), 6·62 (br, 1), 8·20 (s, 1).

2.1.2.3 1-(*Propylsulfonyl*)*-1*H-*pyrazol-3-yl methanesulfonate* (***21***). To a solution of 1*H*-pyrazol-3-yl methanesulfonate (0·50 g, 0·31 mmol) in dichloromethane (15 ml) at 0°C was added triethylamine (0·60 ml, 4·3 mmol) followed by propanesulfonyl chloride (0·48 ml, 4·3 mmol). The reaction mixture was stirred at room temperature overnight; then washed with water, dried (sodium sulfate), filtered and the solvent was removed with a rotary evaporator. The residue was purified by flash chromatography on silica gel (ethyl acetate + hexane (25 + 75 by volume) as eluant) to afford 0·61 g of **21** as a colorless oil.

[^{1}H]NMR (deuterochloroform): δ 1·04 (t, 3), 1·75 (m, 2), 3·37 (s, 3), 3·44 (m, 2), 6·37 (d, 1), 8·00 (d, 1).

2.2 Biological tests

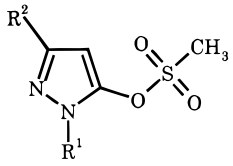
The biological test methods were those described previously.[1]

3 RESULTS AND DISCUSSION

Table 1 shows the insecticidal activity of a series of 1,5-substituted pyrazole methanesulfonates. Despite the fact that these compounds do not fit our model they still showed insecticidal activity. In fact **4** showed a very high level of activity. In a later soil test this compound demonstrated corn root protection for 21 days at 600 mg litre^{-1}. To allay any doubts we had about the regiochemistry of the condensation of propanesulfonyl hydrazide with ethyl acetoacetate, a single-crystal X-ray analysis of the pyrazolone was performed. This analysis confirmed that **4** was a 1,5-substituted pyrazole as shown.

While these compounds showed interesting levels of insecticidal activity they proved unsuitable as candidates for agricultural utility, since they were found to be unstable. Once we had the 1,3-substituted pyrazole

TABLE 1
Insecticidal Activity of 1,5-Substituted Pyrazole Methanesulfonates



			LD_{90} (*mg litre*$^{-1}$)		
No.	R^1	R^2	D.u.h.[a]	N.l.[b]	N.c.[c]
1	$CONHC_2H_5$	CH_3	92	n.d.[d]	n.d.
2	CONH-*i*-C_3H_7	CH_3	46	n.d.	n.d.
3	CONH-*i*-C_3H_7	NH_2	>250	n.d.	n.d.
4	$SO_2C_3H_7$	CH_3	<0·5	<2·5	5·5
5	$SO_2C_3H_7$	CH_2OCH_3	320	n.d.	n.d.
6	$SO_2C_3H_7$	C_2H_5	58	10	16
7	$SO_2C_3H_7$	Ph	35	n.d.	n.d.
8	$SO_2C_4H_9$	CH_3	8·4	n.d.	n.d.
9	SO_2-*i*-C_4H_9	CH_3	38	9.3	19

[a] *Diabrotica undecimpunctata howardi.*
[b] *Nilaparvata lugens.*
[c] *Nephotettix cincticeps.*
[d] Not determined.

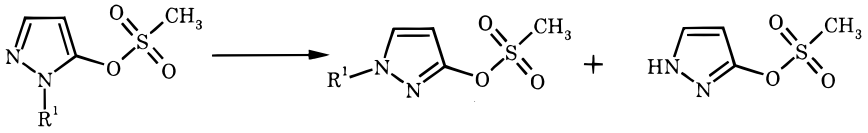
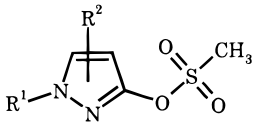


Fig. 4. Reaction of 1,3-substituted pyrazole methanesulfonates at room temperature.

methanesulfonates in hand we were able to determine that the 1,5-isomers upon standing at room temperature were completely converted to two products within a few weeks (Fig. 4). In addition to hydrolysis of the pyrazole-carbonyl or sulfonyl bond to give the pyrazole sulfonate unsubstituted on nitrogen, we observed rearrangement to the corresponding 1,3-isomer. The presence of the 1,3-isomers may explain the level of insecticidal activity demonstrated by the 1,5-isomers.

Table 2 shows the insecticidal activity of a series of the 1,3-substituted pyrazole methanesulfonates. These compounds showed higher levels of activity than the

TABLE 2
Insecticidal Activity of 1,3-Substituted Pyrazole Methanesulfonates



			LD_{90} (*mg litre*$^{-1}$)		
No.	R^1	R^2	D.u.h.[a]	N.l.[b]	N.c.[c]
10	$CON(CH_3)_2$	H	<0·5	n.d.[d]	n.d.
11	CONH-*i*-C_3H_7	H	0·6	<2·5	8·3
12	CONH-*s*-C_4H_9	H	<0·5	<2·5	<2·5
13	CONH-*t*-C_4H_9	H	34	n.d.	n.d.
14	$CONH(CH_3)CH_2CN$	H	<0·5	n.d.	n.d.
15	$CONHCH(CH_3)C_3H_7$	H	<0·5	n.d.	76
16	$CON(CH_3)$-*i*-C_3H_7	H	7·0	n.d.	n.d.
17	$CON(CH_3)$-*s*-C_4H_9	H	8·0	n.d.	n.d.
18	CONH-*i*-C_3H_7	5-NH_2	970	n.d.	n.d.
19	CONH-*i*-C_3H_7	5-CH_3	170	n.d.	n.d.
20	SO_2CH_3	H	<0·5	<2·5	<2·5
21	$SO_2C_3H_7$	H	<0·5	<2·5	<2·5
22	SO_2-*i*-C_3H_7	H	<0·5	<2·5	n.d.
23	SO_2-*i*-C_4H_9	H	<0·5	n.d.	n.d.
24	SO_2CH_3	4-Br	8·1	n.d.	n.d.
25	$SO_2C_2H_5$	5-CH_3	8·4	< 2·5	n.d.
26	$SO_2C_3H_7$	5-NH_2	<0·5	<2·5	5·0
27	$SO_2C_3H_7$	5-CH_3	<0·5	<2·5	3·4
28	$SO_2C_3H_7$	4-CH_3	<0·5	6·0	<2·5
29	$SO_2C_3H_7$	5-CF_3	>1000	n.d.	n.d.
30	$SO_2C_3H_7$	5-SCH_3	1·8	<2·5	6·7
31	$SO_2C_3H_7$	5-C_2H_5	1·8	<2·5	18
32	$SO_2C_3H_7$	5-*c*-C_3H_7	6·8	<2·5	6·8
33	$SO_2C_3H_7$	5-*i*-C_3H_7	1·2	n.d.	n.d.
34	$SO_2C_3H_7$	5-CH_2OCH_3	<0·5	n.d.	6·9
35	$SO_2C_3H_7$	5-CH_2SCH_3	3·3	n.d.	n.d.
36	$SO_2C_3H_7$	5-$CH_2CO_2CH_3$	<0·5	n.d.	n.d.
37	SO_2-*i*-C_3H_7	5-CH_3	1·7	<2·5	n.d.
38	$SO_2C_4H_9$	5-CH_3	1·3	<2·5	42
39	SO_2-*i*-C_4H_9	5-CH_3	<0·5	<2·5	2·5
40	SO_2-*i*-C_4H_9	5-SCH_3	1·3	n.d.	n.d.
41	$SO_2CH_2SO_2CH_3$	5-CH_3	900	n.d.	n.d.

[a] *Diabrotica undecimpunctata howardi.*
[b] *Nilaparvata lugens.*
[c] *Nephotettix cincticeps.*
[d] Not determined.

TABLE 3
Rat Oral Approximate Lethal Dose Measurements for Selected 1,3-Substituted Pyrazole Methanesulfonates

No.	*ALD* ($mg\ kg^{-1}$)
11	>100
12	>100
20	≦12
21	≦1
22	≦12
23	3
26	≦12
27	≦12
28	≦12
30	100

corresponding 1,5-isomers. The carboxamides of this series (**10**–**19**) were more active than the corresponding pyridines. The activity trends followed the pyridine series with the *sec*-butyl compound (**12**) being the most active. These observations are consistent with our model.

The sulfonamides of this series (**20**–**41**) demonstrated very high levels of activity. It cannot be seen from these data, but from the results of a soil activity test **21** possessed the highest level of activity. It demonstrated corn root protection for 70 days at 300 mg $litre^{-1}$. This was more active than 6-alkylthiopyridine methanesulfonate (**II**). Additional substituents on the pyrazole ring reduced activity. Especially detrimental was the trifluoromethyl group in the 5-position (**29**). The electron-withdrawing nature of this substituent enhances the leaving group ability of the pyrazole and may accelerate hydrolysis of either the sulfonamide or sulfonate ester. While our model failed to predict that the *n*-propyl compound (**21**) would be more active than a compound containing branching at the appropriate site in the side chain (**23**), it was still successful in predicting high levels of activity for these compounds.

Table 3 shows rat oral approximate lethal dose measurements for selected 1,3-substituted pyrazole methanesulfonates. The carboxamides (**11** and **12**) showed lower levels of acute mammalian toxicity than the sulfonamides. The only sulfonamide (**30**) which showed a level of acute toxicity which would put it in consideration for utility as a rice insecticide performed poorly in more advanced tests.

Compounds **11** and **12** were tested in a 24-h acute static test against aquatic species. For **11** the LC_{50} was estimated to be greater than 10 mg $litre^{-1}$ against *Daphnia magna* Straus. and greater than 0·5 mg $litre^{-1}$ against *Cyprinus carpio* L. (carp). For **12** the numbers were between 0·5 and 10 mg $litre^{-1}$ and 0·05 and 0·5 mg $litre^{-1}$ respectively. These results demonstrate excellent to good levels of aquatic safety.

While the oral ALD results for compounds **20**–**28** were discouraging, we were still considering **23** as a potential soil insecticide. Compounds **12**, **21** and **23** were tested in the Ames mutagenicity test against *Salmonella typhimurium* Castel. & Chalm. Surprising to us were positive results for **21** and **23**. All of the methanesulfonates we had tested (i.e. **II** and selected 6-methylsulfonyloxypyridine-2-carboxamides) had given negative results. These data resulted in us dropping from considering the development of any of the pyrazole sulfonamide methanesulfonates as soil insecticides.

Compound **12** was tested in a paddy rice field test. In contrast to the nursery box application test we had performed with the 6-methylsulfonyloxypyridine-2-carboxamides in which we had used laboratory raised *Nilaparvata lugens* (Staol) and *Laodelphax striatella* (Fall)[1] the natural field population of hoppers was used in this test. Insufficient control was seen on any of the hopper species to warrant continued testing of this compound. Subsequent laboratory testing demonstrated that the wild strain hoppers were less susceptible to these compounds.

4 CONCLUSION

We have developed a model which has allowed us to design highly active pyrazole methanesulfonates. The pyrazole carboxamide methanesulfonates demonstrated insecticidal activity with low levels of acute mammalian toxicity; the pyrazole sulfonamide methanesulfonates possessed extremely high levels of insecticidal activity, but along with acute mammalian toxicity. This model should prove useful in designing other insecticidal sulfonates.

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